

021466



⑪ ⑩ No. 967573

⑫ ISSUED May 13, 1975

⑬ CLASS 260-277.7  
C.R. CL. 260-280  
260-298.3  
260-314.1

⑭ CA

## CANADIAN PATENT

⑮

TETRACYCLIC ANTIINFLAMMATORY AGENTS

THE BRITISH LIBRARY

17 JUL 1975

SCIENCE LIBRARY

⑯

Lombardino, Joseph G., Niantic, Connecticut, U.S.A.

Granted to Pfizer Inc., New York, New York, U.S.A.

⑰

APPLICATION No. 159,762

⑱

FILED Dec. 22, 1972

⑲

PRIORITY DATE

No. OF CLAIMS 2 - No drawing

Best Available Copy

This publication is a photographic reproduction of the specification filed by the applicant for patent of invention. Any spelling or grammatical errors in the specification are the responsibility of the patentee.

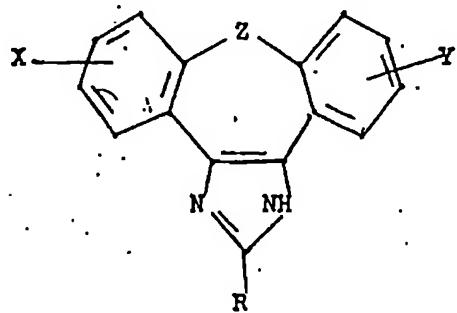
Cette publication est une reproduction photographique du mémoire descriptif déposé par le demandeur d'un brevet d'invention. Le breveté assume la responsabilité de toute erreur orthographique ou grammaticale dans le mémoire descriptif.

967573

This invention relates to tetracyclic imidazoles, and more particularly to a series of 2-substituted dibenzo-[*b,f*]thiepin[4,5-*d*]- and dibenzo[3,4,*d*,7,8]cycloocta[1,2-*d*]-imidazoles and their pharmaceutically acceptable acid addition salts as a novel class of antiinflammatory agents. Synthesis of these compounds is achieved through a condensation of the requisite  $\alpha$ -diketone, and aldehyde and ammonium acetate.

References directed toward polycyclic imidazoles are not common in the chemical literature; Steck and Day, J. Am. Chem. Soc., 65, 452 (1943), in an effort to determine the course of the reaction involved in imidazole formation synthesized a series of phenanthrimidazoles. No utility, however, was disclosed for these compounds.

The tetracyclic antiinflammatory agents of this invention are represented by the formula:



and the pharmaceutically acceptable acid addition salts thereof, where:

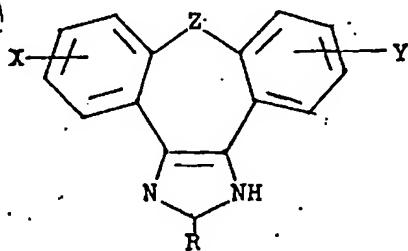
A is  $-\text{CH}_2\text{CH}_2-$  or S;

X and Y are each hydrogen, methyl, methoxy, fluorine, chlorine, bromine or methylthio; and

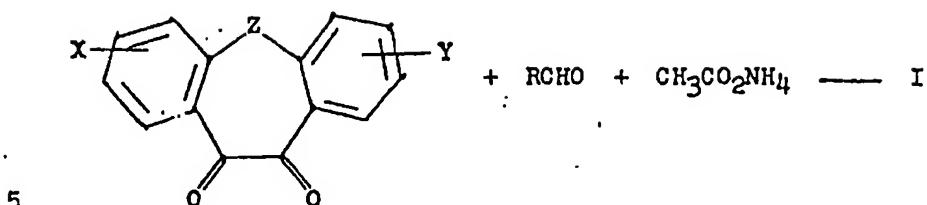
R is trifluoromethyl, pyridyl, naphthyl or phenyl or substituted phenyl where the substituent is methyl, methoxy, fluorine, chlorine, bromine, dimethylamino, carboxy or methylthio.

10 Of particular interest are congeners wherein Z is ethylene, X and Y are hydrogen and R is phenyl, 3-pyridyl or trifluoromethyl, and those wherein Z is sulphur, X and Y are hydrogen and R is p-methoxyphenyl, 3-pyridyl, trifluoromethyl or p-carboxyphenyl.

15 In accordance with the process for preparing the tetracyclicimidazoles of the present invention of formula I:



20 25 wherein Z, X, Y and R are as previously indicated, the following scheme is illustrative:



The above illustrated reaction is conducted under reaction conditions which are essentially those as employed by Davidson, *et al.*, *J. Org. Chem.*, 2, 319 (1937), and comprises heating a mixture of an  $\alpha$ -diketone, an aldehyde or derivative thereof and ammonium acetate in a solvent of glacial acetic acid. As much as five to ten fold excess of ammonium acetate can be employed. The amount of aldehyde used in relation to the diketone can vary from an equimolar amount to as much as a 100% excess.

15 In general, reflux temperatures are considered desirable although lower temperatures with correspondingly longer reaction periods are operable. When said reflux temperatures are employed reaction times of 1-12 hours are adequate to yield the desired product.

20 A convenient method for isolation of the product comprises dilution of the reaction mixture with water followed by neutralization with ammonium hydroxide to a pH of approximately 7. The resulting precipitate is then filtered, dried and recrystallized from an appropriate solvent.

25 The requisite  $\alpha$ -diketones wherein X and Y are as defined and Z is ethylene are synthesized according to the method taught by Leonard, *et al.*, *J. Am. Chem. Soc.*, 77, 5078 (1955). Further,  $\alpha$ -diketones wherein X and Y are as indicated and Z is sulphur are prepared by selenium dioxide 30 oxidation of the corresponding monoketones which, in turn,

are made according to the procedure as taught by Jilek, et al., Monatsh. Chem., 96, 201 (1965). The appropriate aldehydes are either commercially available or easily prepared by one skilled in the art according to the methods as outlined by Carnduff, Quart. Rev., 20, 169 (1966).

A characteristic of the compounds of the present invention is the acidic nature of the imidazole hydrogen and the property to form salts with basic reagents such as alkali metal hydroxides, alkoxides or hydrides and alkali earth metal hydroxides.

As has been previously mentioned, the compounds of the present invention, in addition to forming salts with basic reagents, can also, as previously mentioned form acid addition salts. Said compounds of the present invention are converted to the acid addition salts by interaction of the base with an acid either in an aqueous or nonaqueous medium. In a similar manner, treatment of the acid addition salts with an equivalent amount of an aqueous base solution, e.g., alkali metal hydroxides, alkali metal carbonates and alkali metal bicarbonates or with an equivalent amount of a metal cation which forms an insoluble precipitate with the acid anion, results in a regeneration of the free base form. Such conversions are best carried out as rapidly as possible and under temperature, conditions and method dictated by the stability of said basic products. The bases thus regenerated may be reconverted to the same or a different acid addition salt.

In the utilization of the chemotherapeutic activity of those compounds of the present invention which form salts, it is preferred, of course, to use pharmaceutically

acceptable salts. Although water-insolubility, high toxicity, or lack of crystalline nature may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water insoluble or toxic salts can be converted to the corresponding pharmaceutically acceptable bases by decomposition of the salt as described above, or alternately they can be converted to any desired pharmaceutically acceptable acid addition salt.

Examples of acids which provide pharmaceutically acceptable anions are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, or sulfurous, phosphoric, acetic, lactic, citric, tartaric, succinic, maleic, and gluconic acids.

As previously indicated, the tetracyclicimidazoles of the present invention are all readily adapted to therapeutic use as antiinflammatory agents in mammals. Outstanding for their effectiveness in this regard are the following agents: 8,9-dihydro-2-phenyldibenzo[3,4,7,8]cycloocta[1,2-d]imidazole (I: Z =  $\text{CH}_2\text{CH}_2$ ; X, Y = H and R = Ø), 8,9-dihydro-2-(3-pyridyl)-dibenzo[3,4,7,8]cycloocta[1,2-d]imidazole (I: Z =  $\text{CH}_2\text{CH}_2$ ; X, Y = H and R = 3-pyridyl), 8,9-dihydro-2-trifluoromethylidibenzo[3,4,7,8]cycloocta[1,2-d]imidazole (I: Z =  $\text{CH}_2\text{CH}_2$ ; X, Y = H and R =  $\text{CF}_3$ ), 2-trifluoromethyl-dibenzo[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = H and R =  $\text{CF}_3$ ), 2-(p-methoxyphenyl)dibenzo[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = H and R = p-MeOC<sub>6</sub>H<sub>4</sub>), 2-(3-pyridyl)dibenzo[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = H and R = 3-pyridyl) and 2-(p-carboxyphenyl)dibenzo[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = H and R = p-HO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>).

A standard procedure for detecting and comparing

antiinflammatory activity of compounds in this series and for which there is an excellent correlation with human efficacy is the carrageenin rat foot edema test of Winter, et al., Proc. Soc. Exp. Biol., 111, 544 (1962), whereby unanesthetized adult albino rats of 150-190 g. body weight are each numbered, weighed and marked with ink on the right lateral malleolus. One hour after administration of the drug by gavage, edema is introduced by injection of 0.05 ml. of 1% solution of carrageenin into the plantar tissue of the marked paws. Immediately thereafter, the volume of the injected paw is measured. The increase in volume three hours after the injection of carrageenin constitutes the individual response. Compounds are considered active if the difference in response between a control and the drug being tested is significant. Standard compounds are phenylbutazone at 33 mg./kg. and acetylsalicylic acid at 100 mg./kg., both with oral administration.

The tetracyclicimidazoles and the pharmaceutically acceptable salts thereof, which are useful antiinflammatory agents, may be administered either as individual therapeutic agents or as mixtures of therapeutic agents. They may be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk sugar or certain types of clay, etc. They may be administered orally in the form of elixirs or oral suspensions with the active ingredients combined with emulsifying and/or suspending agents. They may be injected parenterally, and

for this use they, or appropriate derivatives, may be prepared in the form of sterile aqueous solutions. Such aqueous solutions should be suitably buffered, if necessary, and should contain other solutes such as saline or glucose  
5 to render them isotonic.

Although the use of the present invention is directed toward the treatment of mammals in general, the preferred subject is humans. In determining an efficacious dose for human therapy, results of animal testing are frequently extrapolated and a correlation is assumed between animal test behavior and proposed human dosage. When a commercially employed standard is available, the dose level of the clinical candidate in humans is frequently determined by comparison of its performance with the standard in an animal test.  
10  
15 For example, phenylbutazone is employed as a standard anti-inflammatory agent and is administered to humans at the rate of 100 to 400 mg. daily. It is assumed, then, that if compounds of the present invention have activity comparable to phenylbutazone in the test assay, that similar doses will provide comparable responses in humans.  
20

Obviously, the physician will ultimately determine the dosage which will be most suitable for a particular individual, and it will vary with the age, weight and response of the particular patient as well as with the nature  
25 and extent of the symptoms and the pharmacodynamic characteristics of the particular agent to be administered. Generally, small doses will be administered initially, with a gradual increase in the dosage until the optimum level is determined. It will often be found that when the composition  
30 is administered orally, larger quantities of the active

ingredient will be required to produce the same level as produced by a small quantity administered parenterally.

Having full regard for the foregoing factors, an effective daily dosage of the compounds of the present invention in humans is approximately 0.1 to 1.0 g. per day, with a preferred range of about 0.2 to 0.8 g. per day in single or divided doses, or at about 3 to 10 mg./kg. of body weight will effectively alleviate inflammation in human subjects prone to said disorder. These values are illustrative, and there may, of course, be individual cases where higher or lower dose ranges are merited.

The following examples are provided solely for the purpose of illustration and are not to be construed as limitations of this invention, many variations of which are possible without departing from the spirit or scope thereof.

EXAMPLE I

8,9-Dihydro-2-(*p*-methoxyphenyl)dibenzo[3,4,7,8]cyclo-octa[1,2-d]imidazole (I: Z = -CH<sub>2</sub>CH<sub>2</sub>-; X, Y = H and R = p-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>)

To a solution of 1.5 g. (6.4 m moles) of 11,12-dihydrocycloocta[a,e]dibenzene-5,6-dione in 50 ml. of dry glacial acetic acid contained in a three-necked flask and under a nitrogen atmosphere is added 3.0 g. of ammonium acetate. To the resulting dark yellow solution is added, dropwise, 1.1 g. (7.7 m molea) of *p*-methoxybenzaldehyde in 10 ml. of dry glacial acetic acid. The reaction mixture is heated to reflux overnight and is then cooled, poured into 300 ml. of ice - water and the pH adjusted to 7.0 by the addition of ammonium hydroxide solution. The resulting precipitate is filtered, dried and recrystallized from

benzene, 385 mg., m.p. 318-320° C. A second recrystallization from benzene provided the analytical sample, m.p. 321-323° C.

Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O: C, 81.8; H, 5.7;  
N, 8.0.

Found: C, 81.2; H, 5.9;  
N, 7.6.

#### EXAMPLE II

Starting with 11,12-dihydrocycloocta[a,e]dibenzene-5,6-dione and the requisite aldehyde, and repeating the procedure of Example I, the following compounds are prepared:

8,9-dihydro-2-phenyldibenzo[3,4,7,8]cycloocta-[1,2-d]imidazole, m.p. 334-335° C.;

8,9-dihydro-2-(p-bromophenyl)dibenzo[3,4,7,8]-cycloocta[1,2-d]imidazole, m.p. 358-360° C.;

8,9-dihydro-2-(p-chlorophenyl)dibenzo[3,4,7,8]-cycloocta[1,2-d]imidazole, m.p. 347-348° C.;

8,9-dihydro-2-(3-pyridyl)dibenzo[3,4,7,8]cycloocta[1,2-d]imidazole, m.p. 285-286° C.;

8,9-dihydro-2-(p-methylthiophenyl)dibenzo[3,4,7,8]-cycloocta[1,2-d]imidazole, m.p. 329-331° C.;

8,9-dihydro-2-trifluoromethylbibenzo[3,4,7,8]-cycloocta[1,2-d]imidazole, m.p. 290-292° C.;

8,9-dihydro-2-(p-carboxyphenyl)dibenzo[3,4,7,8]-cycloocta[1,2-d]imidazole, m.p. 340-342° C.; and

8,9-dihydro-2-(p-dimethylaminophenyl)dibenzo[3,4,7,8]-cycloocta[1,2-d]imidazole, m.p. 308-311° C.

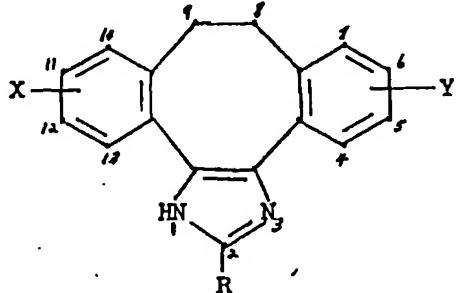
#### EXAMPLE III

The procedure of Example I is again repeated,

967573

starting with the appropriately substituted  $\alpha$ -diketone  
and aldehyde, to provide the following congeners:

5



	<u>X</u>	<u>Y</u>	<u>R</u>	<u>X</u>	<u>Y</u>	<u>R</u>
10	H	H	2-C <sub>5</sub> H <sub>4</sub> N	H	7-CH <sub>3</sub>	m-BrC <sub>6</sub> H <sub>4</sub>
	H	H	4-C <sub>5</sub> H <sub>4</sub> N	H	7-CH <sub>3</sub>	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	H	H	$\alpha$ -C <sub>10</sub> H <sub>7</sub>	H	7-CH <sub>3</sub>	m-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	H	H	$\beta$ -C <sub>10</sub> H <sub>7</sub>	H	7-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
15	H	H	$\underline{\alpha}$ -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub>	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	H	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub>	$\underline{\alpha}$ -FC <sub>6</sub> H <sub>4</sub>
	H	H	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub>	p-FC <sub>6</sub> H <sub>4</sub>
	H	H	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	4-CH <sub>3</sub> O	C <sub>6</sub> H <sub>5</sub>
20	H	H	$\underline{\alpha}$ -FC <sub>6</sub> H <sub>4</sub>	H	4-CH <sub>3</sub> O	$\underline{\alpha}$ -CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	H	H	m-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	H	4-CH <sub>3</sub> O	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	H	m-BrC <sub>6</sub> H <sub>4</sub>	H	4-CH <sub>3</sub> O	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	H	H	$\underline{\alpha}$ -CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> O	C <sub>6</sub> H <sub>5</sub>
25	H	5-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	5-CH <sub>3</sub> O	$\underline{\alpha}$ -FC <sub>6</sub> H <sub>4</sub>
	H	5-CH <sub>3</sub>	CF <sub>3</sub>	H	5-CH <sub>3</sub> O	m-FC <sub>6</sub> H <sub>4</sub>
	H	5-CH <sub>3</sub>	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> O	m-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
	H	5-CH <sub>3</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> O	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
30	H	6-CH <sub>3</sub>	3-C <sub>5</sub> H <sub>4</sub> N	H	5-CH <sub>3</sub> O	p-BrC <sub>6</sub> H <sub>4</sub>
	H	6-CH <sub>3</sub>	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> O	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>

	X	Y	R	X	Y	R
	H	6-CH <sub>3</sub>	p-FC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> O	$\underline{o}$ -CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	H	6-CH <sub>3</sub>	m-FC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> O	CF <sub>3</sub>
	H	6-CH <sub>3</sub>	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	H	6-CH <sub>3</sub> O	C <sub>6</sub> H <sub>5</sub>
5	H	4-CH <sub>3</sub>	3-C <sub>5</sub> H <sub>4</sub> N	H	6-CH <sub>3</sub> O	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	H	4-CH <sub>3</sub>	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	6-CH <sub>3</sub> O	$\underline{o}$ -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	4-CH <sub>3</sub>	p-FC <sub>6</sub> H <sub>4</sub>	H	6-CH <sub>3</sub> O	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	4-CH <sub>3</sub>	m-FC <sub>6</sub> H <sub>4</sub>	H	6-CH <sub>3</sub> O	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	H	4-CH <sub>3</sub>	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> O	CF <sub>3</sub>
10	H	7-CH <sub>3</sub>	$\alpha$ -C <sub>10</sub> H <sub>7</sub>	H	7-CH <sub>3</sub> O	$\underline{o}$ -FC <sub>6</sub> H <sub>4</sub>
	H	7-CH <sub>3</sub>	2-C <sub>5</sub> H <sub>4</sub> N	H	7-CH <sub>3</sub> O	m-FC <sub>6</sub> H <sub>4</sub>
	H	7-CH <sub>3</sub> O	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> O	$\beta$ -C <sub>10</sub> H <sub>7</sub>
	H	7-CH <sub>3</sub> O	p-BrC <sub>6</sub> H <sub>4</sub>	H	4-C1	CF <sub>3</sub>
	H	7-CH <sub>3</sub> O	$\underline{o}$ -CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	H	4-C1	C <sub>6</sub> H <sub>5</sub>
15	H	7-CH <sub>3</sub> O	3-C <sub>5</sub> H <sub>4</sub> N	H	4-C1	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	H	7-CH <sub>3</sub> O	$\underline{o}$ -HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	H	4-C1	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	4-F	CF <sub>3</sub>	H	5-C1	$\underline{o}$ -C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
	H	4-F	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	5-C1	m-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
	H	4-F	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	5-C1	$\underline{o}$ -FC <sub>6</sub> H <sub>4</sub>
20	H	4-F	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	5-C1	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	4-F	C <sub>6</sub> H <sub>5</sub>	H	5-C1	$\underline{o}$ -CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	H	5-F	C <sub>6</sub> H <sub>5</sub>	H	6-C1	CF <sub>3</sub>
	H	5-F	CF <sub>3</sub>	H	6-C1	C <sub>6</sub> H <sub>5</sub>
	H	5-F	3-C <sub>5</sub> H <sub>4</sub> N	H	6-C1	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
25	H	5-F	$\underline{o}$ -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	6-C1	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	5-F	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	7-C1	CF <sub>3</sub>
	H	5-F	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	7-C1	$\underline{o}$ -BrC <sub>6</sub> H <sub>4</sub>
	H	5-F	p-BrC <sub>6</sub> H <sub>4</sub>	H	7-C1	m-BrC <sub>6</sub> H <sub>4</sub>
	H	5-F	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	H	7-C1	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
30	H	5-F	p-FC <sub>6</sub> H <sub>4</sub>	H	7-C1	C <sub>6</sub> H <sub>5</sub>

967573

	<u>X</u>	<u>Y</u>	<u>R</u>	<u>X</u>	<u>Y</u>	<u>R</u>
	H	6-F	CF <sub>3</sub>	H	4-Br	CF <sub>3</sub>
	H	6-F	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	4-Br	C <sub>6</sub> H <sub>5</sub>
	H	6-F	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	4-Br	p-CH <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>
5	H	6-F	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	5-Br	CF <sub>3</sub>
	H	6-F	C <sub>6</sub> H <sub>5</sub>	H	5-Br	o-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	H	7-F	α-C <sub>10</sub> H <sub>7</sub>	H	5-Br	o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	7-F	β-C <sub>10</sub> H <sub>7</sub>	H	5-Br	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	7-F	C <sub>6</sub> H <sub>5</sub>	H	5-Br	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>
10	H	7-F	m-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	H	5-Br	p-FC <sub>6</sub> H <sub>4</sub>
	H	7-F	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	6-Br	CF <sub>3</sub>
	H	7-F	o-FC <sub>6</sub> H <sub>4</sub>	H	6-Br	C <sub>6</sub> H <sub>5</sub>
	H	7-F	p-FC <sub>6</sub> H <sub>4</sub>	H	6-Br	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	7-Br	CF <sub>3</sub>	H	6-CH <sub>3</sub> S	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
15	H	7-Br	3-C <sub>5</sub> H <sub>4</sub> N	H	7-CH <sub>3</sub> S	CF <sub>3</sub>
	H	7-Br	4-C <sub>5</sub> H <sub>4</sub> N	H	7-CH <sub>3</sub> S	o-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
	H	7-Br	C <sub>6</sub> H <sub>5</sub>	H	7-CH <sub>3</sub> S	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
	H	7-Br	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> S	p-BrC <sub>6</sub> H <sub>4</sub>
	H	4-CH <sub>3</sub> S	CF <sub>3</sub>	H	7-CH <sub>3</sub> S	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
20	H	4-CH <sub>3</sub> S	α-C <sub>10</sub> H <sub>7</sub>	H	7-CH <sub>3</sub> S	2-C <sub>5</sub> H <sub>4</sub> N
	H	4-CH <sub>3</sub> S	β-C <sub>10</sub> H <sub>7</sub>	H	7-CH <sub>3</sub> S	3-C <sub>5</sub> H <sub>4</sub> N
	H	4-CH <sub>3</sub> S	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> S	4-C <sub>5</sub> H <sub>4</sub> N
	H	4-CH <sub>3</sub> S	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>			
	H	5-CH <sub>3</sub> S	C <sub>6</sub> H <sub>5</sub>			
25	H	5-CH <sub>3</sub> S	o-FC <sub>6</sub> H <sub>4</sub>			
	H	5-CH <sub>3</sub> S	m-FC <sub>6</sub> H <sub>4</sub>			
	H	5-CH <sub>3</sub> S	p-FC <sub>6</sub> H <sub>4</sub>			
	H	5-CH <sub>3</sub> S	m-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>			
	H	5-CH <sub>3</sub> S	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>			
30	H	6-CH <sub>3</sub> S	CF <sub>3</sub>			

967573

X	Y	R
H	6-CH <sub>3</sub> S	α-C <sub>10</sub> H <sub>7</sub>
H	6-CH <sub>3</sub> S	β-C <sub>10</sub> H <sub>7</sub>
H	6-CH <sub>3</sub> S	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>

5

EXAMPLE IV

8,9-Dihydro-2-trifluoromethyl-5,12-dichlorodibenzo-[3,4,7,8]cycloocta[1,2-d]imidazole (I: Z = -CH<sub>2</sub>CH<sub>2</sub>-;  
X, Y = Cl; R = CF<sub>3</sub>)

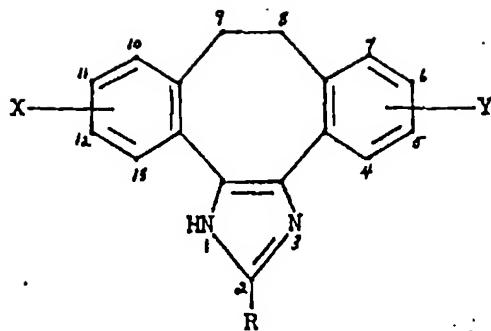
A solution of 3.04 g. (10 m moles) of 11,12-dihydro-  
10 3,8-dichlorocycloocta[a,e]dibenzene-5,6-dione in 100 ml. of  
anhydrous glacial acetic acid, under a nitrogen atmosphere,  
is treated with 4.7 g. of ammonium acetate followed by 4.3  
g. (30 m moles) of trifluoroacetaldehyde ethyl hemiacetal in  
50 ml. of the same solvent. The resulting solution is heated  
15 to reflux for 3 hours, an additional 4.3 g. of the hemiacetal  
added and heating continued for 3 hours more. The reaction  
mixture is cooled, poured into a mixture of ice and water  
and the pH adjusted to 7 using concentrated ammonium hydrox-  
ide solution. The crude product is filtered, dried and puri-  
20 fied by recrystallization several times from toluene.

EXAMPLE V

Starting with the requisite 11,12-dihydrocyclo-  
octa[a,e]dibenzene-5,6-dione and aldehyde, and following  
the procedure of Example IV, the following tetracyclic-  
25 imidazole analogs are synthesized:

967573

5



	X	Y	R	X	Y	R
10	13-CH <sub>3</sub>	5-CH <sub>3</sub>	CF <sub>3</sub>	10-F	6-CI	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	13-CH <sub>3</sub>	5-CH <sub>3</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	10-F	6-CI	o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	13-CH <sub>3</sub>	5-CH <sub>3</sub>	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	10-F	6-CI	α-C <sub>10</sub> H <sub>7</sub>
	13-CH <sub>3</sub>	5-CH <sub>3</sub>	o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	10-F	6-CI	CF <sub>3</sub>
	13-CH <sub>3</sub>	5-CH <sub>3</sub>	p-FC <sub>6</sub> H <sub>4</sub>	13-CI	6-CI	CF <sub>3</sub>
15	13-CH <sub>3</sub> O	5-CH <sub>3</sub>	m-FC <sub>6</sub> H <sub>4</sub>	13-CI	6-CI	3-C <sub>5</sub> H <sub>4</sub> N
	13-CH <sub>3</sub> O	5-CH <sub>3</sub>	3-C <sub>5</sub> H <sub>4</sub> N	13-CI	5-Br	o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	13-CH <sub>3</sub> O	5-CH <sub>3</sub>	4-C <sub>5</sub> H <sub>4</sub> N	13-CI	5-Br	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	13-CH <sub>3</sub> O	5-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	13-CI	5-Br	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	13-CH <sub>3</sub> O	7-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	11-CI	5-Br	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
20	13-CH <sub>3</sub> O	7-CH <sub>3</sub>	CF <sub>3</sub>	11-CI	5-Br	CF <sub>3</sub>
	13-CH <sub>3</sub> O	7-CH <sub>3</sub>	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	11-CI	5-CH <sub>3</sub> O	CF <sub>3</sub>
	12-CH <sub>3</sub> O	7-CH <sub>3</sub>	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	11-CI	5-CH <sub>3</sub> O	C <sub>6</sub> H <sub>4</sub>
	12-CH <sub>3</sub> O	7-CH <sub>3</sub>	α-C <sub>10</sub> H <sub>7</sub>	11-CI	5-CH <sub>3</sub> O	m-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	12-CH <sub>3</sub> O	5-F	CF <sub>3</sub>	11-CI	5-CH <sub>3</sub> O	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
25	12-CH <sub>3</sub> O	5-F	C <sub>6</sub> H <sub>5</sub>	10-Br	5-CH <sub>3</sub> O	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	11-CH <sub>3</sub> O	5-F	2-C <sub>5</sub> H <sub>4</sub> N	10-Br	5-CH <sub>3</sub> O	CF <sub>3</sub>
	11-CH <sub>3</sub> O	5-F	4-C <sub>5</sub> H <sub>4</sub> N	10-Br	5-CH <sub>3</sub> O	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>
	11-CH <sub>3</sub> O	5-F	p-BrC <sub>6</sub> H <sub>4</sub>	10-Br	5-CH <sub>3</sub>	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>
	11-CH <sub>3</sub> O	6-F	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	10-Br	5-CH <sub>3</sub>	CF <sub>3</sub>
30	11-CH <sub>3</sub> O	6-F	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	10-Br	5-CH <sub>3</sub>	m-BrC <sub>6</sub> H <sub>4</sub>

967573

X	Y	R	X	Y	R	
12-CH <sub>3</sub> O	6-F	o-FC <sub>6</sub> H <sub>4</sub>	10-Br	5-CH <sub>3</sub>	m-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	
13-F	6-F	o-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	13-CH <sub>3</sub> S	5-CH <sub>3</sub>	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	
13-F	6-F	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	13-CH <sub>3</sub> S	5-CH <sub>3</sub>	m-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	
5	13-F	6-CI	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	13-CH <sub>3</sub> S	5-CH <sub>3</sub>	CF <sub>3</sub>
13-F	6-CI	m-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	13-CH <sub>3</sub> S	7-F	CF <sub>3</sub>	
13-F	6-CI	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	13-CH <sub>3</sub> S	7-F	C <sub>6</sub> H <sub>5</sub>	
11-F	6-CI	$\beta$ -C <sub>10</sub> H <sub>7</sub>	13-CH <sub>3</sub>	7-F	$\beta$ -C <sub>10</sub> H <sub>7</sub>	
11-F	6-CI	o-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	13-CH <sub>3</sub>	7-F	3-C <sub>5</sub> H <sub>4</sub> N	
10	11-F	6-CI	o-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	13-CH <sub>3</sub>	7-F	4-C <sub>5</sub> H <sub>4</sub> N
11-F	6-CI	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	13-CH <sub>3</sub>	7-F	p-BrC <sub>6</sub> H <sub>4</sub>	
13-CH <sub>3</sub>	5-CI	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	11-CH <sub>3</sub> O	7-Br	o-BrC <sub>6</sub> H <sub>4</sub>	
13-CH <sub>3</sub>	5-CI	p-FC <sub>6</sub> H <sub>4</sub>	11-CH <sub>3</sub> O	7-Br	p-BrC <sub>6</sub> H <sub>4</sub>	
13-CH <sub>3</sub>	5-CI	CF <sub>3</sub>	11-CH <sub>3</sub> O	7-Br	CF <sub>3</sub>	
15	13-CH <sub>3</sub>	5-CI	C <sub>6</sub> H <sub>5</sub>	11-CH <sub>3</sub> O	5-CH <sub>3</sub> S	CF <sub>3</sub>
13-CH <sub>3</sub> S	5-CI	C <sub>6</sub> H <sub>5</sub>	11-CH <sub>3</sub> O	5-CH <sub>3</sub> S	C <sub>6</sub> H <sub>5</sub>	
13-CH <sub>3</sub> S	5-CI	CF <sub>3</sub>	11-CH <sub>3</sub> O	5-CH <sub>3</sub> S	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	
13-CH <sub>3</sub> S	5-CI	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	11-CH <sub>3</sub> O	5-CH <sub>3</sub> S	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	
13-CH <sub>3</sub> S	5-CI	$\alpha$ -C <sub>10</sub> H <sub>7</sub>	11-CH <sub>3</sub> O	7-CH <sub>3</sub> O	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	
20	13-CH <sub>3</sub> S	5-CH <sub>3</sub> S	$\beta$ -C <sub>10</sub> H <sub>7</sub>	11-CH <sub>3</sub> O	7-CH <sub>3</sub> O	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
13-CH <sub>3</sub> S	5-CH <sub>3</sub> S	CF <sub>3</sub>	11-CH <sub>3</sub> O	7-CH <sub>3</sub> O	o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	
10-Br	5-CH <sub>3</sub> S	CF <sub>3</sub>	11-CH <sub>3</sub> O	7-CH <sub>3</sub> O	o-CH <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	
10-Br	5-CH <sub>3</sub> S	2-C <sub>5</sub> H <sub>4</sub> N	11-F	7-Br	o-FC <sub>6</sub> H <sub>4</sub>	
10-Br	5-CH <sub>3</sub> S	4-C <sub>5</sub> H <sub>4</sub> N	11-F	7-Br	p-FC <sub>6</sub> H <sub>4</sub>	
25	10-Br	7-Br	C <sub>6</sub> H <sub>5</sub>			
10-Br	7-Br	m-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>				
10-Br	7-Br	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>				
11-F	7-Br	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>				

EXAMPLE VI30      2-Tri fluoromethyl dibenzo[b,f]thienin[1,5-d]imidazole

967573

(I: Z = S; X, Y = H and R =  $\text{F}_3$ )

A mixture of 170 mg. (0.7 m mole) of 10,11-dihydro-  
dibenzo[*b,f*]thiepin-10,11-dione, 300 mg. (2.1 m moles) of tri-  
fluoroacetaldehyde ethyl hemiacetal and 4.0 g. of ammonium  
acetate in 40 ml. of anhydrous glacial acetic acid is heated  
to the reflux temperature for one hour. An additional 170 mg.  
of diketone and 300 mg. of hemiacetal in 5 ml. of the same  
solvent are added and the refluxing continued for one more  
hour. The addition is repeated again, and the mixture heated  
at reflux temperatures for 3 hours. The reaction mixture is  
cooled, poured into ice - water and the pH adjusted with am-  
monium hydroxide to 7. The crude product is filtered, dried  
and recrystallized from benzene, 300 mg., m.p. 255-257° C.

Anal. Calcd. for  $\text{C}_{16}\text{H}_{9}\text{N}_2\text{SF}_3$ : C, 60.4; H, 2.8; N,  
15 8.8.

Found: C, 60.4; H, 3.1; N,  
8.6.

EXAMPLE VII

Starting with 10,11-dihydridibenzo[*b,f*]thiepin-10,11-  
20 dione and the appropriate aldehyde and repeating the procedure  
of Example VI, the following compounds are prepared:

2-Phenylbenzo[*b,f*]thiepin-4,5-d<sub>7</sub>imidazole, m.p.  
312° C., dec.;

2-(*p*-methoxyphenyl)dibenzo[*b,f*]thiepin-4,5-d<sub>7</sub>imidaze-  
25 sole, m.p. 300° C., dec.;

2-(*p*-bromophenyl)dibenzo[*b,f*]thiepin-4,5-d<sub>7</sub>imidazole,  
m.p. 334° C., dec.;

2-(*p*-chlorophenyl)dibenzo[*b,f*]thiepin-4,5-d<sub>7</sub>imi-  
dazole, m.p. 323° C., dec.;

30 2-(3-pyridyl)dibenzo[*b,f*]thiepin-4,5-d<sub>7</sub>imidazole,

967573

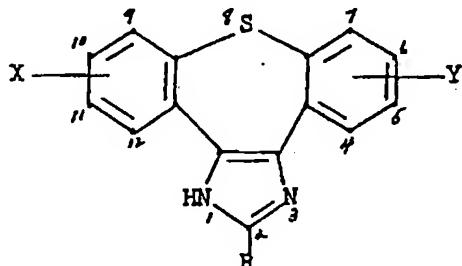
m.p. 230° C., dec.

2-(*p*-carboxyphenyl)dibenzo[*b,f*]thiepin[4,5-*d*]imidazole, m.p. 360° C.; and

2-(*p*-dimethylaminophenyl)dibenzo[*b,f*]thiepin[4,5-*d*]imidazole, m.p. 321° C., dec.

Starting with the appropriately substituted 10,11-dihydrodibenzo[*b,f*]thiepin-10,11-dione and requisite aldehyde, and employing the procedure of Example VI, the following compounds are prepared:

10



15

	<u>X</u>	<u>Y</u>	<u>R</u>	<u>X</u>	<u>Y</u>	<u>R</u>
	H	H	-C <sub>10</sub> H <sub>7</sub>	H	5-CH <sub>3</sub> O	2-C <sub>5</sub> H <sub>4</sub> N
	H	H	-C <sub>10</sub> H <sub>7</sub>	H	5-CH <sub>3</sub> O	4-C <sub>5</sub> H <sub>4</sub> N
	H	H	2-C <sub>5</sub> H <sub>4</sub> N	H	5-CH <sub>3</sub> O	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
20	H	H	p-FC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> O	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	H	H	o-FC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> O	-C <sub>10</sub> H <sub>7</sub>
	H	H	m-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> O	CF <sub>3</sub>
	H	H	o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> O	m-BrC <sub>6</sub> H <sub>4</sub>
	H	H	o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> O	p-BrC <sub>6</sub> H <sub>4</sub>
25	H	H	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> O	o-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
	H	H	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> O	o-FC <sub>6</sub> H <sub>4</sub>
	H	4-CH <sub>3</sub>	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	H	4-F	CF <sub>3</sub>
	H	4-CH <sub>3</sub>	CF <sub>3</sub>	H	4-F	C <sub>6</sub> H <sub>5</sub>
	H	4-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	4-F	3-C <sub>5</sub> H <sub>4</sub> N
30	H	4-CH <sub>3</sub>	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	4-F	4-C <sub>5</sub> H <sub>4</sub> N
	H	4-CH <sub>3</sub>	p-FC <sub>6</sub> H <sub>4</sub>	H	4-F	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>

	X	Y	R	X	Y	R
	H	5-CH <sub>3</sub>	p-FC <sub>6</sub> H <sub>4</sub>	H	6-F	CF <sub>3</sub>
	H	5-CH <sub>3</sub>	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>	H	6-F	o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	5-CH <sub>3</sub>	p-BrC <sub>6</sub> H <sub>4</sub>	H	6-F	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
5	H	5-CH <sub>3</sub>	o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	6-F	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	5-CH <sub>3</sub>	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	6-F	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	H	7-CH <sub>3</sub>	m-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	H	5-CI	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	H	7-CH <sub>3</sub>	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	H	5-CI	$\alpha$ -C <sub>10</sub> H <sub>7</sub>
	H	7-CH <sub>3</sub>	p-C <sub>11</sub> OC <sub>6</sub> H <sub>4</sub>	H	5-CI	$\beta$ -C <sub>10</sub> H <sub>7</sub>
10	H	7-CH <sub>3</sub>	$\alpha$ -C <sub>10</sub> H <sub>7</sub>	H	5-CI	C <sub>6</sub> H <sub>5</sub>
	H	5-CH <sub>3</sub> O	CF <sub>3</sub>	H	5-CI	CF <sub>3</sub>
	H	5-CH <sub>3</sub> O	C <sub>6</sub> H <sub>5</sub>	H	7-CI	CF <sub>3</sub>
	H	7-CI	o-FC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> S	$\alpha$ -C <sub>10</sub> H <sub>7</sub>
	H	7-CI	m-FC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> S	$\beta$ -C <sub>10</sub> H <sub>7</sub>
15	H	7-CI	p-FC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> S	3-C <sub>5</sub> H <sub>4</sub> N
	H	7-CI	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> S	4-C <sub>5</sub> H <sub>4</sub> N
	H	7-CI	m-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> S	CF <sub>3</sub>
	H	4-Br	o-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	H	5-CH <sub>3</sub> S	o-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	H	4-Br	m-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	H	6-CH <sub>3</sub> S	o-BrC <sub>6</sub> H <sub>4</sub>
20	H	4-Br	CF <sub>3</sub>	H	6-CH <sub>3</sub> S	m-BrC <sub>6</sub> H <sub>4</sub>
	H	4-Br	C <sub>6</sub> H <sub>5</sub>	H	6-CH <sub>3</sub> S	m-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>
	H	5-Br	C <sub>6</sub> H <sub>5</sub>	H	6-CH <sub>3</sub> S	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	H	5-Br	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> S	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	H	5-Br	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> S	CF <sub>3</sub>
25	H	5-Br	CF <sub>3</sub>	H	7-CH <sub>3</sub> S	C <sub>6</sub> H <sub>5</sub>
	H	5-Br	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> S	o-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
	H	6-Br	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	7-CH <sub>3</sub> S	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>
	H	6-Br	CF <sub>3</sub>	H	7-CH <sub>3</sub> S	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	H	6-Br	o-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>			
30	H	6-Br	p-C <sub>1</sub> C <sub>6</sub> H <sub>4</sub>			

967573

<u>X</u>	<u>Y</u>	<u>R</u>
H	5-CH <sub>3</sub> S	p-FC <sub>6</sub> H <sub>4</sub>
H	5-CH <sub>3</sub> S	2-C <sub>5</sub> H <sub>4</sub> N

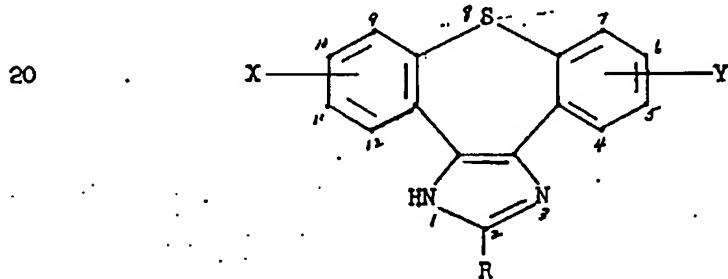
EXAMPLE IX

5      2-Phenyl-5,11-dichlorodibenzo[*b,f*]thiepin[4,5-*d*]imide  
dazole (I: Z = S; X, Y = Cl; R = C<sub>6</sub>H<sub>5</sub>)

A mixture of 3.08 (0.01 mole) of 2,8-dichloro-10,  
11-dihydrobenzo[*b,f*]thiepin-10,11-dione, 7.0 g. of ammonium  
acetate and 1.28 g. (0.012 mole) of benzaldehyde in 85 ml.  
10     of dry glacial acetic acid is heated to reflux for 12 hours.  
The reaction mixture is cooled, poured into ice - water and  
ammonium hydroxide added until a pH of 7 is achieved. The  
precipitate is suction filtered and dried. Recrystallization  
from benzene provides the desired purified product.

15      EXAMPLE X

Employing the aforescribed procedure of Example  
IX, and starting with the requisite ketone and aldehyde, the  
following analogs are synthesized:



<u>X</u>	<u>Y</u>	<u>R</u>	<u>X</u>	<u>Y</u>	<u>R</u>
12-CH <sub>3</sub>	4-CH <sub>3</sub>	CF <sub>3</sub>	12-Cl	4-Cl	p-ClC <sub>6</sub> H <sub>4</sub>
12-CH <sub>3</sub>	4-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	12-Cl	4-Cl	p-FC <sub>6</sub> H <sub>4</sub>
12-CH <sub>3</sub>	4-CH <sub>3</sub>	3-C <sub>5</sub> H <sub>4</sub> N	12-Cl	4-Cl	o-BrC <sub>6</sub> H <sub>4</sub>
12-CH <sub>3</sub>	4-CH <sub>3</sub>	4-C <sub>5</sub> H <sub>4</sub> N	10-Cl	4-Cl	3-C <sub>5</sub> H <sub>4</sub> N
30    10-CH <sub>3</sub>	4-CH <sub>3</sub>	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	10-Cl	4-Cl	C <sub>6</sub> H <sub>5</sub>

967573

X	Y	R	X	Y	R	
10-CH <sub>3</sub>	4-CH <sub>3</sub>	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	10-C1	5-C1	C <sub>6</sub> H <sub>5</sub>	
10-CH <sub>3</sub>	5-CH <sub>3</sub>	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	10-C1	5-C1	m-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	
10-CH <sub>3</sub>	5-CH <sub>3</sub>	CF <sub>3</sub>	10-C1	5-C1	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	
5	10-CH <sub>3</sub>	5-CH <sub>3</sub>	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	10-Br	5-C1	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>
	10-OCH <sub>3</sub>	5-CH <sub>3</sub>	α-C <sub>10</sub> H <sub>7</sub>	10-Br	5-C1	m-BrC <sub>6</sub> H <sub>4</sub>
	10-OCH <sub>3</sub>	5-CH <sub>3</sub>	β-C <sub>10</sub> H <sub>7</sub>	10-Br	5-C1	CF <sub>3</sub>
	10-OCH <sub>3</sub>	5-CH <sub>3</sub>	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	10-Br	5-CH <sub>3</sub> O	CF <sub>3</sub>
	10-OCH <sub>3</sub>	5-F	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	10-Br	5-CH <sub>3</sub> O	C <sub>6</sub> H <sub>5</sub>
10	10-OCH <sub>3</sub>	5-F	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	9-Br	5-CH <sub>3</sub> O	m-FC <sub>6</sub> H <sub>4</sub>
	10-OCH <sub>3</sub>	5-F	o-FC <sub>6</sub> H <sub>4</sub>	9-Br	5-CH <sub>3</sub> O	p-FC <sub>6</sub> H <sub>4</sub>
	10-OCH <sub>3</sub>	5-F	m-C1C <sub>6</sub> H <sub>4</sub>	9-Br	5-CH <sub>3</sub> O	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	11-F	5-F	p-BrC <sub>6</sub> H <sub>4</sub>	9-Br	7-CH <sub>3</sub>	CF <sub>3</sub>
	11-F	5-F	CF <sub>3</sub>	9-Br	7-CH <sub>3</sub>	o-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
15	11-F	5-CH <sub>3</sub> O	CF <sub>3</sub>	10-CH <sub>3</sub> S	7-CH <sub>3</sub>	3-C <sub>5</sub> H <sub>4</sub> N
	11-F	5-CH <sub>3</sub> O	C <sub>6</sub> H <sub>5</sub>	10-CH <sub>3</sub> S	7-CH <sub>3</sub>	4-C <sub>5</sub> H <sub>4</sub> N
	11-F	5-CH <sub>3</sub> O	p-FC <sub>6</sub> H <sub>4</sub>	10-CH <sub>3</sub> S	7-CH <sub>3</sub>	α-C <sub>10</sub> H <sub>7</sub>
	11-F	5-CH <sub>3</sub> O	o-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	10-CH <sub>3</sub> S	5-Br	α-C <sub>10</sub> H <sub>7</sub>
	11-F	5-CH <sub>3</sub> O	o-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	10-CH <sub>3</sub> S	5-Br	CF <sub>3</sub>
20	9-F	5-CH <sub>3</sub> O	2-C <sub>5</sub> H <sub>4</sub> N	10-CH <sub>3</sub> S	5-Br	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	9-F	5-CH <sub>3</sub> O	4-C <sub>5</sub> H <sub>4</sub> N	10-CH <sub>3</sub> S	5-Br	o-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
	9-F	7-CH <sub>3</sub> O	m-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	9-F	5-Br	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	9-F	7-CH <sub>3</sub> O	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	9-F	5-Br	p-BrC <sub>6</sub> H <sub>4</sub>
	9-F	7-CH <sub>3</sub> O	p-BrC <sub>6</sub> H <sub>4</sub>	9-F	5-CH <sub>3</sub> S	m-FC <sub>6</sub> H <sub>4</sub>
25	12-C1	7-CH <sub>3</sub> O	m-BrC <sub>6</sub> H <sub>4</sub>	9-F	5-CH <sub>3</sub> S	p-FC <sub>6</sub> H <sub>4</sub>
	12-C1	7-CH <sub>3</sub> O	β-C <sub>10</sub> H <sub>7</sub>	9-F	5-CH <sub>3</sub> S	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
	12-C1	7-CH <sub>3</sub> O	CF <sub>3</sub>	9-F	5-CH <sub>3</sub> S	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
	11-CH <sub>3</sub>	5-F	CF <sub>3</sub>	10-CH <sub>3</sub> O	7-CH <sub>3</sub> S	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
	11-CH <sub>3</sub>	5-F	C <sub>6</sub> H <sub>5</sub>	10-CH <sub>3</sub> O	7-CH <sub>3</sub> S	m-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>
30	11-CH <sub>3</sub>	5-F	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	10-CH <sub>3</sub> O	7-CH <sub>3</sub> S	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>

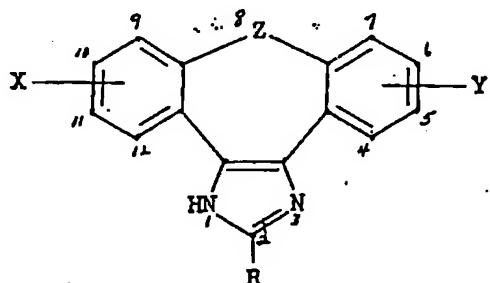
967573

<u>X</u>	<u>Y</u>	<u>R</u>	<u>X</u>	<u>Y</u>	<u>R</u>
11-CH <sub>3</sub>	5-F	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	10-CH <sub>3</sub> O	7-CH <sub>3</sub> S	o-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
11-CH <sub>3</sub>	5-Cl	CF <sub>3</sub>	10-CH <sub>3</sub> O	6-Br	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>
11-CH <sub>3</sub>	5-Cl	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	10-Br	6-Br	CF <sub>3</sub>
5 11-CH <sub>3</sub>	5-Cl	m-BrC <sub>6</sub> H <sub>4</sub>	10-Br	6-Br	o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
12-F	5-Cl	p-BrC <sub>6</sub> H <sub>4</sub>	10-Br	6-Br	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
12-F	5-Cl	2-C <sub>5</sub> H <sub>4</sub> N	10-Br	6-Br	o-BrC <sub>6</sub> H <sub>4</sub>
12-F	5-Cl	3-C <sub>5</sub> H <sub>4</sub> N	10-Br	6-Br	m-ClC <sub>6</sub> H <sub>4</sub>
10-CH <sub>3</sub> S	5-Cl	2-C <sub>5</sub> H <sub>4</sub> N			
10 10-CH <sub>3</sub> S	5-Cl	CF <sub>3</sub>			
10-CH <sub>3</sub> S	5-Cl	C <sub>6</sub> H <sub>5</sub>			
10-CH <sub>3</sub> S	7-CH <sub>3</sub> S	C <sub>6</sub> H <sub>5</sub>			
10-CH <sub>3</sub> S	7-CH <sub>3</sub> S	CF <sub>3</sub>			
10-CH <sub>3</sub> S	7-CH <sub>3</sub> S	p-FC <sub>6</sub> H <sub>4</sub>			

15           EXAMPLE XI

Employing the carageenin rat foot edema test as a measure of anti-inflammatory activity, the following representative tetracyclicimidazoles were found to have the indicated activity at the specified dose:

20



25

<u>Activity</u>						
<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R</u>	<u>%Inhibition</u>	<u>Dose mg./kg., P.O.</u>	
H	H	-CH <sub>2</sub> CH <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub>	46 ✓	33	
H	H	-CH <sub>2</sub> CH <sub>2</sub> -	p-ClC <sub>6</sub> H <sub>4</sub>	19	33	
30 H	H	-CH <sub>2</sub> CH <sub>2</sub> -	3-C <sub>5</sub> H <sub>4</sub> N	21	33	

967573

				<u>Activity</u>	
	X	Y	Z	R	% Inhibition      Dose mg./kg., P.O.
	H	H	-CH <sub>2</sub> CH <sub>2</sub> -	p-CH <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	20      33
	H	H	-CH <sub>2</sub> CH <sub>2</sub> -	CF <sub>3</sub>	20      33
5	H	H	-CH <sub>2</sub> CH <sub>2</sub> -	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	11      33
	H	H	S	C <sub>6</sub> H <sub>5</sub>	19      33
	H	H	S	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	35      33
	H	H	S	p-BrC <sub>6</sub> H <sub>4</sub>	13      33
	H	H	S	3-C <sub>5</sub> H <sub>4</sub> N	25      33
10	H	S	S	CF <sub>3</sub>	36      33
	H	S	S	CF <sub>3</sub>	15      10
	H	S	S	p-HO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	28      33
	phenylbutazone			(55)	33 ✓

EXAMPLE XII

15      8,9-Dihydro-2-(p-methoxyphenyl)dibenzo[3,4,7,8]cyclo-

octa[1,2-d]imidazole hydrochloride

To a warm solution of 3.5 g. (0.01 mole) of 8,9-dihydro-2-(p-methoxyphenyl)dibenzo[3,4,7,8]cycloocta[1,2-d]imidazole in 40 ml. of absolute methanol is added gaseous hydrochloride until the resulting precipitate of the hydrochloride salt ceases to form. The suspension is cooled in ice and the precipitate filtered and dried. An equal volume of diethyl ether is added to the filtrate, resulting in the precipitation of a second crop of the desired hydrochloride salt. The two fractions are combined and recrystallized from ethanol.

In an analogous manner, the compounds of the present invention are converted to their pharmaceutically acceptable acid addition salts.

967573

EXAMPLE XIII

Suspension

A suspension of 2-phenyldibenzo[*b,f*]thiepin[4,5-*d*]-imidazole is prepared with the following composition:

5	Effective ingredient	100.00 g.
	70% Aqueous sorbitol	741.29 g.
	Glycerine, U.S.P.	185.35 g.
	Gum acacia (10% solution)	100.00 ml.
	Polyvinylpyrrolidone	0.50 g.
10	Distilled water	sufficient to make 1 liter

To this suspension, various sweeteners and flavorants are added to improve the palatability of the suspension. The suspension contains approximately 100 mg. of effective agent per milliliter.

15

EXAMPLE XIV

Solid Dispersion

A solid dispersion containing 20% 2-trifluoromethyl-dibenzo[*b,f*]thiepin[4,5-*d*]imidazole and 80% polyethylene glycol 6000 (PEG 6000) is prepared by adding in small portions and with constant stirring 100 g. of the imidazole to 500 g. of PEG 6000 heated to 70° C. When all the compound is added, the melt is "flash cooled" by cooling in an ice bath and the solidified product reduced to a fine powder and passed through a 100 mesh sieve. The material not passing through is recycled through the melting process.

EXAMPLE XV

Tablets

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated:

Sucrose, U.S.P. 80.3

967573

Tapioca starch 13.2

Magnesium stearate 6.5

Into this tablet base there is blended sufficient  
2, trifluoromethylidibenzo/b,f/thiepin/4,5-d/imidazole to  
5 provide tablets containing 20, 100 and 250 mg. of active  
ingredient per tablet. The compositions are each compressed  
into tablets, each weighing 360 mg., by conventional means.

EXAMPLE XVI

Capsules

10 A blend is prepared containing the following  
ingredients:

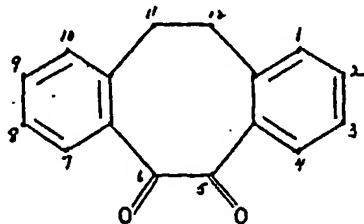
	Calcium carbonate, U.S.P.	17.6
	Dicalcium phosphate	18.8
	Magnesium trisilicate, U.S.P.	5.2
15	Lactose, U.S.P.	5.2
	Potato starch	5.2
	Magnesium stearate A	0.8
	Magnesium stearate B	0.35

To this blend is added sufficient 8,9-dihydro-  
20 2-phenyldibenzo/3,4,7,8/cycloocta/1,2-d/imidazole to pro-  
vide capsules containing 50, 200 and 400 mg. of active ingre-  
dient per capsule. The compositions are filled into conven-  
tional hard gelatin capsules in the amount of 500 mg. per  
capsule.

25 Preparation A

(a) 5,6,11,12-Tetrahydrodibenzo/a,e/cyclooctene-5,6-dione

30

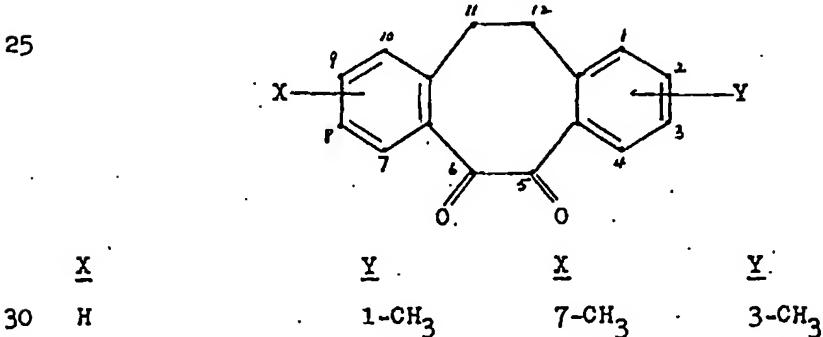


To a suspension of 23.2 g. (0.209 mole) of selenium dioxide in 500 ml. of dry glacial acetic acid, under a nitrogen atmosphere and heated to 80° C., is added dropwise 42.0 g. (0.19 mole) of 5,6,11,12-tetrahydrobenzo $\langle a,e \rangle$ cyclooctene-5-one in 250 ml. of the same solvent. The reaction temperature is raised to 110° C. and maintained at this temperature for 5-6 hours. The mixture is cooled, poured slowly into 2500 ml. of ice - water and extracted several times with ethyl acetate.

The organic layer is back-washed with a saturated sodium bicarbonate solution and dried over calcium sulfate. The calcium sulfate is filtered and the filtrate evaporated to dryness, leaving a yellow semi-solid, which on recrystallization from ethanol provided the desired product in three crystallization fractions, 3.8 g., 21.3 g. and 3.5 g., m.p.'s 130-132° C., 126-129° C. and 130-131° C., respectively. The three crops are combined and used without further purification.

Leonard, et al., J. Am. Chem. Soc., 77, 5078 (1955), reports a melting point of 131-132° C. for this material, prepared by a different method.

(b) The following 5,6,11,12-tetrahydronbenzo $\langle a,e \rangle$ cyclooctene-5,6-diones, not previously reported in the chemical literature, are synthesized by the selenium dioxide oxidation of the corresponding monoketone:



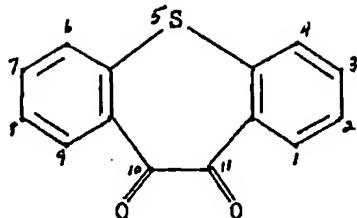
967573

	<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
	H	2-CH <sub>3</sub>	7-CH <sub>3</sub> O	3-CH <sub>3</sub>
	H	3-CH <sub>3</sub>	7-CH <sub>3</sub> O	1-CH <sub>3</sub>
	H	4-CH <sub>3</sub>	8-CH <sub>3</sub> O	1-CH <sub>3</sub>
5	H	1-CH <sub>3</sub> O	8-CH <sub>3</sub> O	3-F
	H	2-CH <sub>3</sub> O	9-CH <sub>3</sub> O	3-F
	H	3-CH <sub>3</sub> O	9-CH <sub>3</sub> O	2-F
	H	4-CH <sub>3</sub> O	8-CH <sub>3</sub> O	2-F
	H	1-F	7-F	2-F
10	H	2-F	7-F	2-Cl
	H	3-F	9-F	2-Cl
	H	4-F	10-F	2-Cl
	H	1-Cl	7-Cl	2-Cl
	H	2-Cl	7-Cl	3-Br
15	H	3-Cl	9-Cl	3-Br
	H	4-Cl	9-Cl	3-CH <sub>3</sub> O
	H	1-Br	10-Br	3-CH <sub>3</sub> O
	H	2-Br	10-Br	3-CH <sub>3</sub>
	H	3-Br	7-CH <sub>3</sub> S	3-CH <sub>3</sub>
20.	H	4-Br	7-CH <sub>3</sub> S	1-F
	H	1-CH <sub>3</sub> S	7-CH <sub>3</sub>	1-F
	H	2-CH <sub>3</sub> S	7-CH <sub>3</sub>	3-Cl
	H	3-CH <sub>3</sub> S	7-CH <sub>3</sub> S	3-Cl
	H	4-CH <sub>3</sub> S	7-CH <sub>3</sub> S	3-CH <sub>3</sub> S
25	10-Br	3-CH <sub>3</sub> S	9-CH <sub>3</sub> O	1-Br
	10-Br	1-Br	9-CH <sub>3</sub> O	3-CH <sub>3</sub> S
	9-F	1-Br	9-CH <sub>3</sub> O	1-CH <sub>3</sub> O

Preparation B(a) 10,11-Dihydrodibenzo[5,6]thiepin-10,11-dione

967573

5



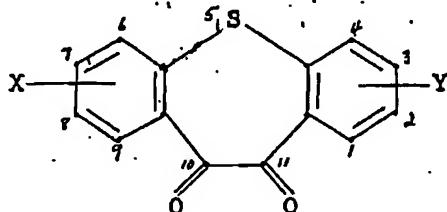
A mixture of 50 mg. (0.22 m mole) of 10,11-dihydrodibenz[b,f]thiepin-10-one and 27 mg. (0.24 m mole) of selenium dioxide in 15 ml. of dry glacial acetic acid is  
10 heated at 80° C. until a solution is effected. The reaction temperature is then raised to 110° C. and maintained for 2 hours. The reaction mixture is filtered, poured into water and extracted with ethyl acetate. The organic layer is concentrated to dryness and the semi-solid triturated with hot benzene. Removal of the benzene provides the desired product  
15 as a yellow solid, 38 mg., m.p. 116-126° C. The analytical sample is triturated with diethyl ether, m.p. 120-126° C.

Anal. Calcd. for C<sub>14</sub>H<sub>8</sub>O<sub>2</sub>S: C, 70.0; H, 3.3.

Found: C, 70.0; H, 3.5.

20 Following the above described oxidation procedure the following substituted 10,11-dihydrodibenz[b,f]thiepin-10,11-diones, not previously known in the literature, are prepared:

25



30

X	Y	X	Y
H	1-CH <sub>3</sub>	6-F	2-CH <sub>3</sub> O
H	2-CH <sub>3</sub>	9-Cl	2-CH <sub>3</sub> O

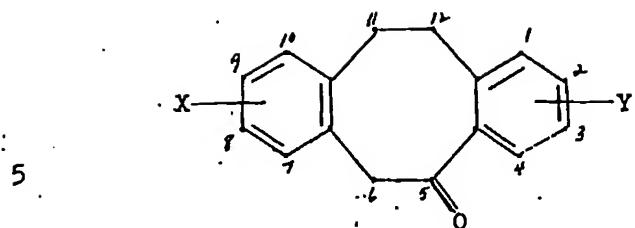
967573

	X	Y	X	Y
	H	4-CH <sub>3</sub>	9-Cl	1-Cl
	H	2-CH <sub>3</sub> O	7-Cl	1-Cl
	H	4-CH <sub>3</sub> O	7-Cl	2-Cl
5	H	1-F	7-Br	2-Cl
	H	3-F	7-Br	2-CH <sub>3</sub> O
	H	2-Cl	6-Br	2-CH <sub>3</sub> O
	H	4-Cl	6-Br	4-CH <sub>3</sub>
	H	1-Br	7-CH <sub>3</sub> S	4-CH <sub>3</sub>
10	H	2-Br	7-CH <sub>3</sub> S	2-Br
	H	3-Br	6-F	2-Br
	H	2-CH <sub>3</sub> S	6-F	2-CH <sub>3</sub> S
	H	3-CH <sub>3</sub> S	8-CH <sub>3</sub>	2-F
	H	4-CH <sub>3</sub> S	8-CH <sub>3</sub>	2-Cl
15	9-CH <sub>3</sub>	1-CH <sub>3</sub>	9-F	2-Cl
	7-CH <sub>3</sub>	1-CH <sub>3</sub>	7-CH <sub>3</sub> S	2-Cl
	7-CH <sub>3</sub>	2-CH <sub>3</sub>	7-CH <sub>3</sub> S	4-CH <sub>3</sub> S
	7-CH <sub>3</sub> O	2-CH <sub>3</sub>	7-CH <sub>3</sub> O	4-CH <sub>3</sub> S
	7-CH <sub>3</sub> O	2-F	7-CH <sub>3</sub> O	3-Br
20	8-F	2-F	7-Br	3-Br
	8-F	2-CH <sub>3</sub> O		

Preparation C11,12-Dihydrocycloocta[*a,e*]dibenzen-5(6H)-ones

The following cycloocta[*a,e*]dibenzen-5(6H)-ones,  
25 previously unreported in the chemical literature, are prepared according to the procedure as taught by Leonard, *et al.*, *J. Am. Chem. Soc.*, 77, 5078 (1955), and comprises cyclization of the appropriate 2-phenylethylphenylacetic acid with polyphosphoric acid at steam bath temperatures for  
30 5-6 hours:

967573



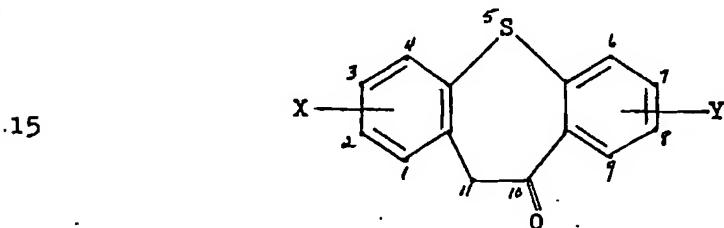
	<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
	H	1-CH <sub>3</sub>	H	1-Br
	H	2-CH <sub>3</sub>	H	2-Br
10	H	3-CH <sub>3</sub>	H	3-Br
	H	4-CH <sub>3</sub>	H	4-Br
	H	1-CH <sub>3</sub> O	H	1-CH <sub>3</sub> S
	H	2-CH <sub>3</sub> O	H	2-CH <sub>3</sub> S
	H	3-CH <sub>3</sub> O	H	3-CH <sub>3</sub> S
15	H	4-CH <sub>3</sub> O	H	4-CH <sub>3</sub> S
	H	1-F	7-CH <sub>3</sub>	3-CH <sub>3</sub>
	H	2-F	7-CH <sub>3</sub> O	3-CH <sub>3</sub>
	H	3-F	7-CH <sub>3</sub> O	1-CH <sub>3</sub>
	H	4-F	8-CH <sub>3</sub> O	1-CH <sub>3</sub>
20	H	1-Cl	8-CH <sub>3</sub> O	3-F
	H	2-Cl	9-CH <sub>3</sub> O	3-F
	H	3-Cl	9-CH <sub>3</sub> O	2-F
	H	4-Cl	8-CH <sub>3</sub> O	2-F
	7-F	2-F	9-Cl	3-CH <sub>3</sub> O
25	7-F	2-Cl	10-Br	3-CH <sub>3</sub> O
	9-F	2-Cl	10-Br	3-CH <sub>3</sub>
	10-F	2-Cl	7-CH <sub>3</sub> S	3-CH <sub>3</sub>
	7-Cl	2-Cl	7-CH <sub>3</sub> S	1-F
	7-Cl	3-Br	7-CH <sub>3</sub>	1-F
30	9-Cl	3-Br	7-CH <sub>3</sub>	3-Cl

967573

	<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
	7-CH <sub>3</sub> S	3-CH <sub>3</sub> S	7-CH <sub>3</sub> S	3-Cl
	10-Br	3-CH <sub>3</sub> S	9-CH <sub>3</sub> O	1-Br
	10-Br	1-Br	9-CH <sub>3</sub> O	3-CH <sub>3</sub> S
5	9-F	1-Br	9-CH <sub>3</sub> O	1-CH <sub>3</sub> O

Preparation D10,11-Dihydrodibenzo[b,f]thiepin-10-ones

Employing the procedure as taught by Jilek, et al., Monatsh. Chem., 96, 201 (1965), the following dibenzo[b,f]thiepin-10-ones are prepared via cyclization of the requisite 2-phenylthiophenylacetic acid using polyphosphoric acid at 125° C. for 1-2 hours:



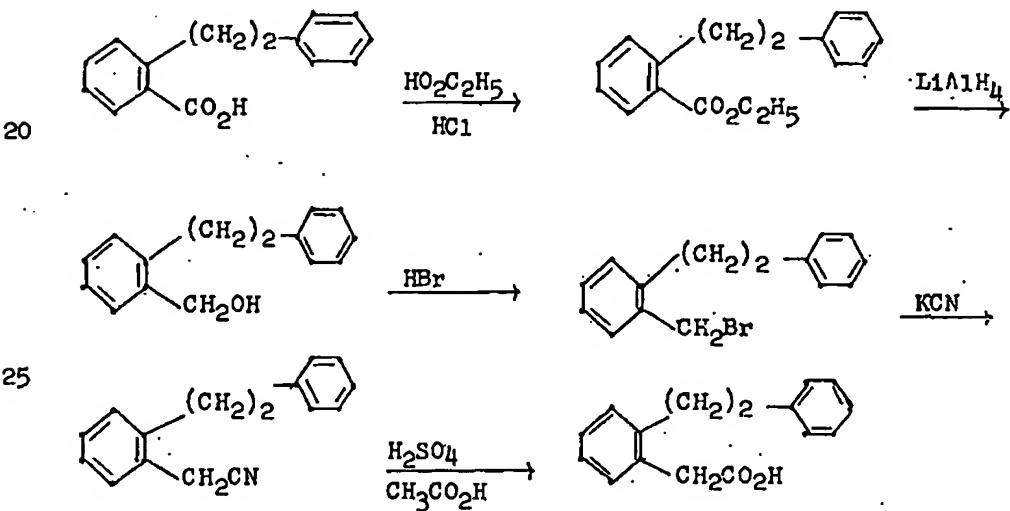
	<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
	H	9-CH <sub>3</sub>	4-F	8-CH <sub>3</sub>
20	H	8-CH <sub>3</sub>	1-Cl	8-CH <sub>3</sub>
	H	8-CH <sub>3</sub> O	1-Cl	9-Cl
	H	6-CH <sub>3</sub> O	3-Cl	9-Cl
	H	9-F	3-Cl	8-Cl
	H	7-F	3-Br	8-Cl
25	3-Br	8-CH <sub>3</sub> O	4-Br	8-CH <sub>3</sub> O
	H	9-Br	4-Br	6-CH <sub>3</sub>
	3-CH <sub>3</sub> S	6-CH <sub>3</sub>	3-CH <sub>3</sub> S	8-Br
	H	7-Br	4-F	8-Br
	H	8-CH <sub>3</sub> S	4-F	8-CH <sub>3</sub> S
30	H	7-CH <sub>3</sub> S	2-CH <sub>3</sub>	8-F

X	Y	X	Y
H	6-CH <sub>3</sub> S	2-CH <sub>3</sub>	8-Cl
1-CH <sub>3</sub>	9-CH <sub>3</sub>	1-F	8-Cl
3-CH <sub>3</sub>	9-CH <sub>3</sub>	3-CH <sub>3</sub> S	8-Cl
5 3-CH <sub>3</sub>	8-CH <sub>3</sub>	3-CH <sub>3</sub> S	6-CH <sub>3</sub> S
3-CH <sub>3</sub> O	8-CH <sub>3</sub>	3-CH <sub>3</sub> O	6-CH <sub>3</sub> S
3-CH <sub>3</sub> O	8-F	3-CH <sub>3</sub> O	7-Br
2-F	8-F	3-Br	7-Br
2-F	8-CH <sub>3</sub> O		

10

Preparation E2-Phenylethylphenylacetic Acids

The above-mentioned 2-phenylethylphenylacetic acids are synthesized according to the sequence of reactions as taught by Leonard, *et al.*, *J. Am. Chem. Soc.*, 77, 5078 (1955), wherein, starting with 2-phenylethylbenzoic acid the following reactions are effected:

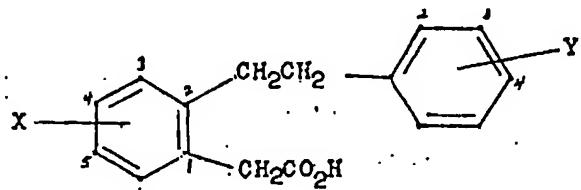


For convenience, the intermediate products are not purified or characterized, but used directly in the next step of the reaction sequence.

967573

Employing the above-described reaction series,  
and starting with the requisite benzoic acid, the following,  
previously unreported 2-phenylethylphenylacetic acids, are  
prepared:

5



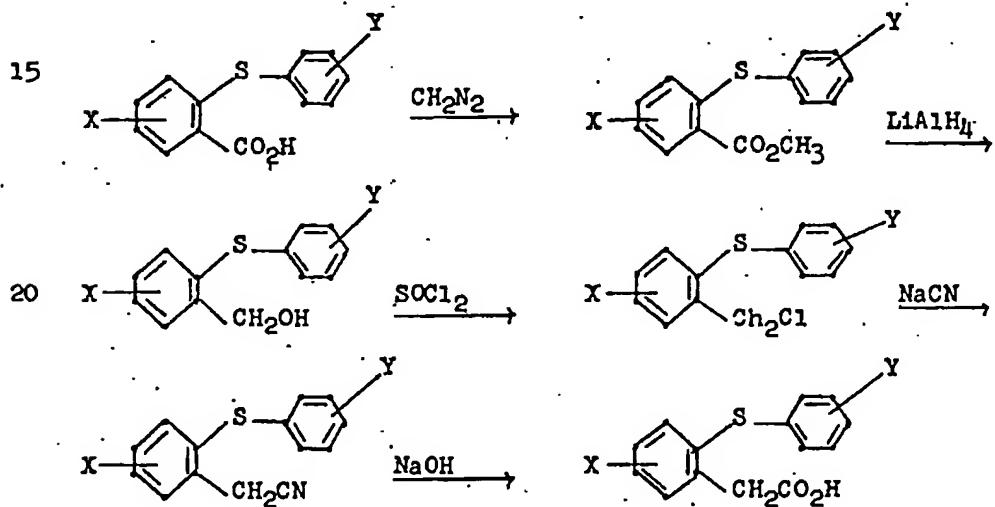
	<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
10	H	2-CH <sub>3</sub>	H	2-CH <sub>3</sub> S
	H	3-CH <sub>3</sub>	H	3-CH <sub>3</sub> S
	H	4-CH <sub>3</sub>	H	4-CH <sub>3</sub> S
	H	2-CH <sub>3</sub> O	6-CH <sub>3</sub>	4-CH <sub>3</sub>
	H	3-CH <sub>3</sub> O	6-CH <sub>3</sub> O	4-CH <sub>3</sub>
15	H	4-CH <sub>3</sub> O	6-CH <sub>3</sub> O	2-CH <sub>3</sub>
	H	2-F	5-CH <sub>3</sub> O	2-CH <sub>3</sub>
	H	3-F	5-CH <sub>3</sub> O	4-F
	H	4-F	4-CH <sub>3</sub> O	4-F
	H	2-Cl	4-CH <sub>3</sub> O	3-F
20	H	3-Cl	5-CH <sub>3</sub> O	3-F
	H	4-Cl	6-F	3-F
	H	2-Br	6-F	3-Cl
	H	3-Br	4-F	3-Cl
	H	4-Br	2-F	3-Cl
25	6-Cl	3-Cl	6-CH <sub>3</sub>	4-Cl
	6-Cl	4-Br	6-CH <sub>3</sub> S	4-Cl
	4-Cl	4-Br	6-CH <sub>3</sub> S	4-CH <sub>3</sub> S
	4-Cl	4-CH <sub>3</sub> O	2-Br	4-CH <sub>3</sub> S
	2-Br	4-CH <sub>3</sub> O	2-Br	2-Br
30	2-Br	4-CH <sub>3</sub>	4-F	2-Br

<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
6-CH <sub>3</sub> S	4-CH <sub>3</sub>	4-CH <sub>3</sub> O	2-Br
6-CH <sub>3</sub> S	2-F	4-CH <sub>3</sub> O	4-CH <sub>3</sub> S
6-CH <sub>3</sub>	2-F	4-CH <sub>3</sub> O	2-CH <sub>3</sub> O

### Preparation F

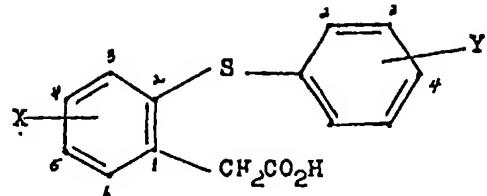
## 2-Phenylthiophenylacetic Acids

The requisite 2-phenylthiophenylacetic acids employed as intermediates leading to the products of the instant invention are prepared by the sequence of reactions 10 as taught by Jilek, et al., Monatsh. Chem., 96, 201 (1965) and Protiva, et al., Csech. Patent 121,337 (C.A. 68, 105247t (1968) and comprises conversion of a 2-phenylthiobenzoic acid to the corresponding phenylacetic acid depicted below.



25 The intermediates are not purified or characterized, but are used directly in the next reaction. In the above-described manner, the following 2-phenylthiophenylacetic acids, not previously described in the chemical literature, are synthesized:

967573



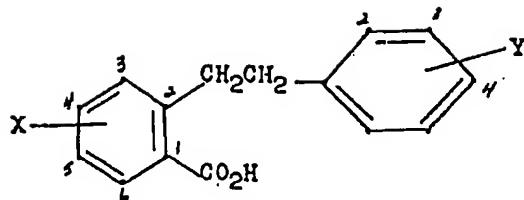
	<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
5	H	3-CH <sub>3</sub>	3-F	4-CH <sub>3</sub> O
	H	4-CH <sub>3</sub>	6-Cl	4-CH <sub>3</sub> O
	H	2-CH <sub>3</sub>	6-Cl	3-Cl
	H	4-CH <sub>3</sub> O	4-Cl	3-Cl
10	H	2-CH <sub>3</sub> O	4-Cl	4-Cl
	H	3-F	4-Br	4-Cl
	H	4-CH <sub>3</sub> S	4-Br	4-CH <sub>3</sub> O
	3-Br	4-CH <sub>3</sub> O	3-Br	2-CH <sub>3</sub>
	H	3-Br	4-CH <sub>3</sub> S	2-CH <sub>3</sub>
15	H	3-CH <sub>3</sub> S	4-CH <sub>3</sub> S	4-Br
	H	2-CH <sub>3</sub> S	3-F	4-Br
	6-CH <sub>3</sub>	3-CH <sub>3</sub>	3-F	4-CH <sub>3</sub> S
	4-CH <sub>3</sub>	3-CH <sub>3</sub>	5-CH <sub>3</sub>	4-F
	4-CH <sub>3</sub>	4-CH <sub>3</sub>	5-CH <sub>3</sub>	4-Cl
20	4-CH <sub>3</sub> O	4-CH <sub>3</sub>	6-F	4-Cl
	4-CH <sub>3</sub> O	4-F	4-CH <sub>3</sub> S	4-Cl
	5-F	4-F	4-CH <sub>3</sub> S	2-CH <sub>3</sub> S
	5-F	4-CH <sub>3</sub> O	4-CH <sub>3</sub> O	2-CH <sub>3</sub> S
	4-CH <sub>3</sub> O	3-Br	4-F	3-Br

25

Preparation G2-Phenylethylbenzoic Acids

The following 2-phenylethylbenzoic acids, not previously reported in the chemical literature, are prepared according to the procedure of Cope, *et al.*, *J. Am. Chem. Soc.*, 73, 1676 (1951) and comprises the red phosphorous - hydriodic acid reduction of the corresponding benzalphthalide:

967573



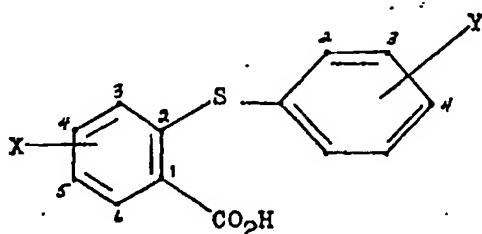
	X	Y	X	Y
5	H	2-CH <sub>3</sub>	H	2-CH <sub>3</sub>
	H	3-CH <sub>3</sub>	H	3-CH <sub>3</sub> S
	H	4-CH <sub>3</sub>	H	4-CH <sub>3</sub> S
	H	2-CH <sub>3</sub> O	6-CH <sub>3</sub>	4-CH <sub>3</sub>
10	H	3-CH <sub>3</sub> O	6-CH <sub>3</sub> O	4-CH <sub>3</sub>
	H	4-CH <sub>3</sub> O	6-CH <sub>3</sub> O	2-CH <sub>3</sub>
	H	3-F	5-CH <sub>3</sub> O	2-CH <sub>3</sub>
	H	4-F	5-CH <sub>3</sub> O	4-F
	H	2-Cl	4-CH <sub>3</sub> O	4-F
15	H	3-Cl	4-CH <sub>3</sub> O	3-F
	H	4-Cl	5-CH <sub>3</sub> O	3-F
	H	2-Br	6-F	3-F
	H	3-Br	6-F	3-Cl
	H	4-Br	4-F	3-Cl
20	6-Cl	3-Cl	3-F	3-Cl
	6-Cl	4-Br	6-CH <sub>3</sub> S	2-F
	4-Cl	4-Br	6-CH <sub>3</sub>	2-F
	6-CH <sub>3</sub> S	4-CH <sub>3</sub> S	6-CH <sub>3</sub>	4-Cl
	3-Br	4-CH <sub>3</sub> S	6-CH <sub>3</sub>	4-Cl
25	3-Br	2-Br	4-CH <sub>3</sub> O	2-Br
	4-F	2-Br	4-CH <sub>3</sub> O	4-CH <sub>3</sub> S
	4-Cl	4-CH <sub>3</sub> O	4-CH <sub>3</sub> O	2-CH <sub>3</sub> O
	3-Br	4-CH <sub>3</sub> O	3-Br	4-CH <sub>3</sub>
	6-CH <sub>3</sub> S	4-CH <sub>3</sub>		

30

Preparation H2-Phenylthiobenzoic Acids

The following 2-phenylthiobenzoic acids, previously unreported in the chemical literature, are synthesized from the commercially available or known thiophenols and *o*-halobenzoic acids according to the method of Protiva,  
 5 et al., Czech. Patent 121,337 (C.A. 68, 105247t; 1968) and  
 Mahishi, et al., J. Karnatak Univ., 2, 50 (1957) (C.A.,  
 53, 14101h; 1959).

10



X

Y

X

Y

15

3-CH<sub>3</sub>

3-F

4-CH<sub>3</sub>O4-CH<sub>3</sub>

6-Cl

4-CH<sub>3</sub>O2-CH<sub>3</sub>

6-Cl

3-Cl

4-CH<sub>3</sub>O

4-Cl

3-Cl

2-CH<sub>3</sub>O

4-Cl

4-Cl

3-F

4-Br

4-Cl

20 4-Br

4-CH<sub>3</sub>O

3-Br

4-CH<sub>3</sub>O

3-Br

3-Br

2-CH<sub>3</sub>4-CH<sub>3</sub>S4-CH<sub>3</sub>S2-CH<sub>3</sub>3-CH<sub>3</sub>S4-CH<sub>3</sub>S

4-Br

2-CH<sub>3</sub>S

3-F

4-Br

25 6-CH<sub>3</sub>3-CH<sub>3</sub>

3-F

4-CH<sub>3</sub>S4-CH<sub>3</sub>3-CH<sub>3</sub>5-CH<sub>3</sub>

4-F

4-CH<sub>3</sub>4-CH<sub>3</sub>5-CH<sub>3</sub>

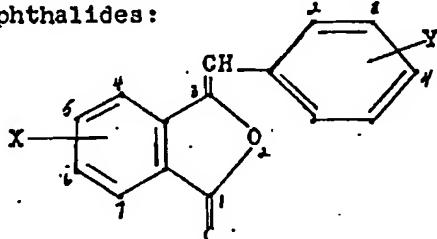
4-Cl

<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
4-CH <sub>3</sub> O	4-CH <sub>3</sub>	6-F	4-Cl
4-CH <sub>3</sub> O	4-F	4-CH <sub>3</sub> S	4-Cl
5-F	4-F	4-CH <sub>3</sub> S	2-CH <sub>3</sub> S
5	5-F	4-CH <sub>3</sub> O	2-CH <sub>3</sub> S
4-CH <sub>3</sub> O	3-Br	3-Br	3-Br

Preparation IBenzalphthalides

Employing the procedures of Weiss, "Organic Syntheses," Coll. Vol. 2, John Wiley & Sons, Inc., New York, N. Y., 1948, page 61, Hrnčiar, *et al.*, *Chem. Zvesti.*, 21, 267 (1967) (*C.A.* 67, 73304v; 1967) and Hrnčiar, *ibid.*, 16, 96 (1962) (*C.A.* 59, 2731; 1963), the following benzalphthalides, not previously reported in the literature, are synthesized either *via* the condensation of the commercially available or known phenylacetic acids and phthalic anhydrides or benzaldehydes and phthalides:

20



25

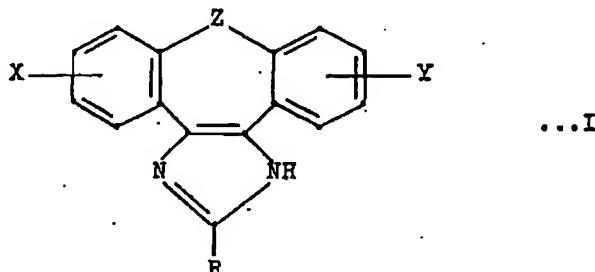
<u>X</u>	<u>Y</u>	<u>X</u>	<u>Y</u>
H	2-CH <sub>3</sub> S	H	3-CH <sub>3</sub> S
7-CH <sub>3</sub>	4-CH <sub>3</sub>	7-Cl	3-Cl
7-CH <sub>3</sub> O	4-CH <sub>3</sub>	7-Cl	4-Br
7-CH <sub>3</sub> O	2-CH <sub>3</sub>	5-Cl	4-Br
6-CH <sub>3</sub> O	2-CH <sub>3</sub>	7-CH <sub>3</sub> S	4-CH <sub>3</sub> S
6-CH <sub>3</sub> O	4-F	4-Br	4-CH <sub>3</sub> S
5-CH <sub>3</sub> O	4-F	4-Br	2-Br
30	5-CH <sub>3</sub> O	5-F	2-Br

967573

	<u>X</u>	<u>Y</u>		<u>X</u>	<u>Y</u>
	6-CH <sub>3</sub> O	3-F		5-Cl	4-CH <sub>3</sub> O
	7-F	3-F		4-Br	4-CH <sub>3</sub> O
	7-F	3-Cl		4-Br	4-CH <sub>3</sub>
5	5-F	3-Cl		7-CH <sub>3</sub> S	4-CH <sub>3</sub>
	4-F	3-Cl		7-CH <sub>3</sub> S	2-F
	7-CH <sub>3</sub>	2-F		7-CH <sub>3</sub>	4-Cl
	7-CH <sub>3</sub> S	4-Cl		5-CH <sub>3</sub> O	2-Br
	5-CH <sub>3</sub> O	4-CH <sub>3</sub> S		5-CH <sub>3</sub> O	2-CH <sub>3</sub> O

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process of preparing a compound selected from those of the formula:



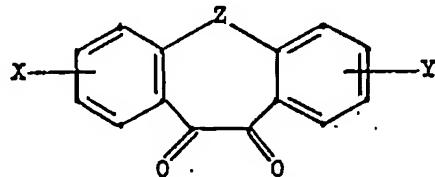
and the pharmaceutically acceptable acid addition salts thereof wherein:

Z is ethylene or sulphur;

X and Y are each the same or different and are hydrogen, methyl, methoxy, fluorine, chlorine, bromine, or methylthio; and

R is trifluoromethyl, pyridyl, naphthyl or phenyl and substituted phenyl wherein said substituent is methyl, methoxy, fluorine, chlorine, bromine, dimethylamino, carboxy or methylthio,

characterized by reacting a diketone of the formula:



wherein X, Y and Z are as defined above,

with an aldehyde of the formula:



wherein R is as defined above,

and ammonium acetate,

and, if desired, preparing the pharmaceutically acceptable salts thereof.

967573

2. Compounds of the Formula I as defined in claim 1, whenever prepared by the process of claim 1 or by an obvious chemical equivalent thereof.

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**